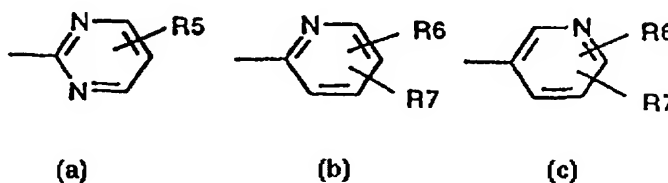
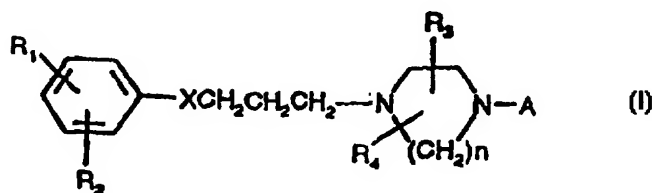




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| | | |
|--|-----------|---|
| (51) International Patent Classification ⁶ : A61K 31/495, 31/505 | A1 | (11) International Publication Number: WO 97/41858 (43) International Publication Date: 13 November 1997 (13.11.97) |
| (21) International Application Number: PCT/SE97/00673 (22) International Filing Date: 22 April 1997 (22.04.97) (30) Priority Data: 9601708-2 6 May 1996 (06.05.96) SE (71) Applicant (for all designated States except US): PHARMACIA & UPJOHN AB [SE/SE]; S-112 87 Stockholm (SE). (72) Inventor; and (75) Inventor/Applicant (for US only): BJÖRK, Anders [SE/SE]; Svalvägen 9, S-237 36 Bjärred (SE). (74) Agent: HEDENSTRÖM, John; Pharmacia & Upjohn AB, P.O. Box 941, S-251 09 Helsingborg (SE). | | (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> |

(54) Title: PYRIDYL- AND PYRIMIDYL-PIPERAZINES IN THE TREATMENT OF SUBSTANCE ABUSE DISORDERS



(57) Abstract

Use of a compound of formula (I) and the pharmaceutically acceptable acid addition salts thereof, wherein R1 is either halogen or hydrogen and R2 is halogen; X is CH₂, O or S; R3 and R4 are the same or different and selected from hydrogen or lower alkyl; n is 2 or 3; A is selected from the pyrimidyl- or pyridyl- groups (a), (b) or (c) wherein R5, R6 and R7 are as defined in the description; for the manufacture of a medicament for the relief or prevention of a withdrawal syndrome resulting from addiction to a drug or substance of abuse or for treatment thereof.

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PYRIDYL- AND PYRIMIDYL-PIPERAZINES IN THE TREAT- MENT OF SUBSTANCE ABUSE DISORDERS

Field of the invention

5 The present invention relates to a new use of certain pyridyl- and
pyrimidylpiperazines substituted in the 1-position of the piperazine ring
with an arylalkyl, an aryloxyalkyl or an arylthioalkyl group in the treatment
of substance abuse disorders. More particularly, this invention relates to the
amelioration of withdrawal symptoms and to modify drug-seeking behav-
10 iour.

Background of the invention

Drug dependency is extremely difficult to escape. This is true whether
the dependency is one based on ethanol, amphetamine, barbiturates, ben-
zodiazepines, cocaine, nicotine, opioids, and phencyclidine or the like. There
15 is thus a need for an agent decreasing or overcoming such addiction and, if
possible reducing or eliminating the symptoms related to the withdrawal of
such drugs or substances of abuse.

Different classes of neuronal receptors and neurotransmitters in the
brain have been implicated in the complex mechanisms underlying for ex-
20 ample the compulsive drinking of alcohol. Experimental findings have fa-
voured the opioid, dopaminergic, serotonergic, and benzodiazepine receptor
subtypes.

Based upon a large number of genetic and pharmacological studies,
serotonin (5-HT) containing neurones in the limbic-midbrain and limbic-
25 forebrain pathways are seemingly involved, in part, in the fundamental
mechanisms underlying for example alcohol drinking.

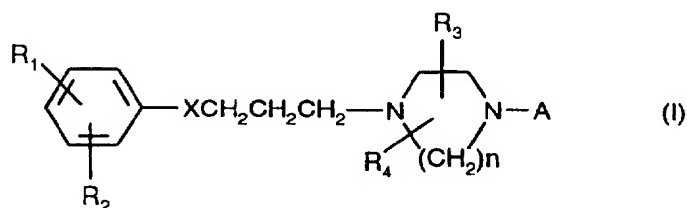
Buspirone (The Merck Index 11th Ed., No. 1493), a partial 5-HT_{1A} ago-
nist, has been found to be effective for the treatment of anxiety. Buspirone
was reported to attenuate significantly the consumption of alcohol by mon-
30 keys. In a clinical trial comparing buspirone to placebo in alcohol-dependent

individuals, there was a lower drop-out rate in the buspirone-treated group, which also reported fewer signs of craving.

Amperozide (The Merck Index 11th Ed., No. 612), a 5-HT₂ antagonist, was reported to significantly attenuate the intake of alcohol in rats without affecting neither consumption of food nor level of body weight (Myers et al., Pharmacol. Biochem. Behav. 43:661-667, 1992). Also the bisphenylalkyl-2-pyridinyl-piperazine derivative FG5893 was reported to have a similar amperozide-like action (Singh et al., Alcohol 10:243-248, 1993).

Summary of the invention

It has now surprisingly been found that the compounds of general formula (I)



and the pharmaceutically acceptable acid addition salts thereof, wherein

R₁ is either halogen or hydrogen and R₂ is halogen;

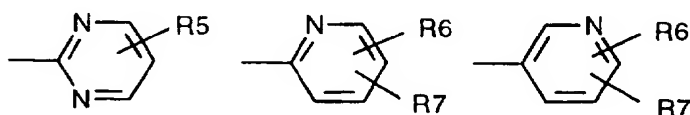
X is CH₂, O or S;

R₃ and R₄ are the same or different and selected from hydrogen or

lower alkyl;

n is 2 or 3;

A is selected from the following pyrimidyl- or pyridyl-groups:



wherein

R₅ is selected from hydrogen, lower alkyl or halogen;

R6 and R7 are the same or different and selected from hydrogen, lower alkyl,

halogen, lower alkoxy, hydroxy, cyano, nitro, trifluoromethyl, COOR8, CONR9R10 or COB;

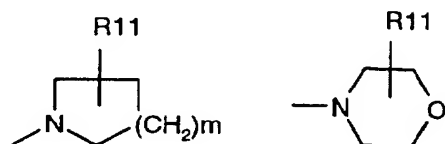
5 wherein

R8 is hydrogen or lower alkyl;

R9 and R10 are the same or different and selected from hydrogen, lower alkyl and cycloalkyl;

B is selected from

10



wherein

m is 1, 2, 3, or 4;

15 R11 is selected from hydrogen or lower alkyl, and when used in the foregoing definitions the term lower alkyl is meant to include straight and branched hydrocarbon groups having from 1 to 5 carbon atoms;

cycloalkyl is meant to include cyclohydrocarbon groups having from 3 to 8 carbon atoms;

20 lower alkoxy is meant to include straight and branched alkoxy groups having from 1 to 5 carbon atoms;

halogen is meant to include F, Cl and Br,

are unexpectedly effective and specific in the treatment of individuals addicted to drugs or substances of abuse, suffering from symptoms related to withdrawal of such drugs or substances. This finding opens up a new method of treating dependence on drugs, such as alcohol, hallucinogens, minor tranquillisers, nicotine, opiates, and stimulants.

25 The aforementioned term "pharmaceutically acceptable acid addition salt" is meant to comprise these salts obtained by treating the base form of the active ingredients of formula (I) with appropriate acids, such as, for ex-

30

ample, inorganic acids, e.g. hydrochloric acid, hydrobromic acid, sulphuric acid, nitric acid, and phosphoric acid, or organic acids, e.g. acetic acid, propanoic acid, glycolic acid, lactic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, and pantoic acid. Conversely, the salt form can
5 be converted into the free base form by treatment with alkali.

The compounds of formula (I) as such as well as their use in other areas of medicine are known from the prior art (see US Pat. No. 5,034,390, which is hereby incorporated by reference).

The preferred substances of the present application have a monoaryl-
10 butyl side chain. The substances according to WO 93/20821 though have a diarylbutyl side chain. This chemical difference cause a significant difference in pharmacological effect for the respective substances - see below under Examples, Table 2.

Detailed description of the invention

15 Twenty years of research has consistently demonstrated that drugs or substances that are abused by man are usually self-administered by laboratory animals. Ethanol, amphetamine, barbiturates, benzodiazepines, cocaine, nicotine, opioids, and phencyclidine and the like are just a few examples of substances abused by man and self-administered in animal models. The
20 value of animal models for investigating the pharmacological and behavioural mechanisms underlying drug dependence has been repeatedly demonstrated. In fact, the animal models are our only recourse for the investigation of compounds to ameliorate or modify drug-seeking behaviour. In relation to this there is considerable experimental evidence supporting
25 that a commonality in the mechanism of the addictive process itself exists in the brain stem which underlies the predilection to abuse the above mentioned drugs.

Drug addiction includes two important characteristics, chronic compulsive or uncontrollable drug use and a withdrawal syndrome when use of
30 drug is stopped. Studies have shown that a person dependent on alcohol often coabuses other substances, for example cocaine. The subjective effects of

these two substances in a dependent individual may often appear to be more similar than they are different. Drugs of abuse have various effects on several neurotransmitters and systems, which ultimately interact to produce the feeling of well-being avidly sought by many individuals. This drive often eventually produces a dependence which has the associated social and medical consequences.

Biological theories of drug reinforcement have emerged that centre around the assumption that drugs of abuse including for example ethanol, cocaine, and nicotine directly or indirectly activate central "reward substrates", that mediate motivated behaviour and reinforcement. A substantial body of evidence implicates the mesocorticolimbic dopamine system in the mediation of acute effects of these drugs of abuse. Hence, there is considerable evidence to suggest a common biological basis for reinforcement from ethanol and other drugs of abuse including cocaine and nicotine.

The present invention relates to a method for treating substance abuse disorders by administering to a patient suffering from abuse a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable acid addition salt thereof. Specifically the invention relates to the relief or prevention of a withdrawal syndrome resulting from addiction to a drug or substance of abuse and/or for the suppression of dependence on drugs or substances of abuse.

Repeated administration to a subject of certain drugs such as alcohol, hallucinogens, minor tranquillisers, nicotine, opiates, and stimulants can lead to physical and/or psychological dependence upon that drug or substance. When the drug or substance of abuse is withdrawn from a dependent subject, the subject develops certain symptoms including sleep and mood disturbance and intense craving for the drug or substance of abuse. These symptoms may be collectively described as a withdrawal syndrome in connection with the present invention.

Although drug treatments for substance abuse disorders are available, these remain largely ineffective and unspecific and, therefore, improvement

is needed. The anorexic and other effects of for example 5-HT reuptake blockers and buspirone constitute a major impediment to their consideration for clinical treatment. The compounds of formula (I) have been found to be both chemically and pharmacologically different from those drugs suggested hitherto for the treatment of drug dependence. Compounds of formula (I) represent a new and novel class of psychotropic agents by having high affinity for both 5-HT_{1A} and 5-HT₂ receptors and low to moderate 5-HT reuptake inhibiting properties.

A preferred compound is (1-[4-(p-fluorophenyl)-butyl]-4-(6-methyl-2-pyridinyl)-piperazine fumarate, hereinafter called Compound A. The following examples are intended to illustrate the present invention without limiting the scope thereof.

Examples

The affinity for Compound A and other drugs acting on serotonergic receptors was determined according to standard procedures. The results are presented in the below Table 1.

Table 1

Drug affinity for serotonergic receptor subtypes.

| Compound | K _i values, nM | |
|--------------------------|---------------------------|---------------------|
| | 5-HT _{1A} | 5-HT _{2A} |
| | Sites ^{a)} | Sites ^{b)} |
| Compound A | 0.9 | 10 |
| Compound B ^{c)} | 1.7 | 1.6 |
| Amperozide | 805 | 16 |
| Buspirone | 15 | 819 |
| FG5893 ^{d)} | 0.7 | 4.0 |

a) Radioligand: ³H-8-OH-DPAT Tissue: Hippocampus

b) Radioligand: ³H-Ketanserin Tissue: Cerebral cortex

c) Chemical name: 1-[4-(p-fluorophenyl)-butyl]-4-(3-ethoxy-2-pyridinyl)-piperazine fumarate

d) Chemical name: 2-[4-[4,4-bis(4-fluorophenyl)butyl]-1-piperazinyl]-3-pyridine-carboxylic acid methyl ester dihydrochloride ethylat

5

To demonstrate that the chemical differences between substances according to WO 93/20821 and the substances according to the present invention cause different pharmacological effects the [3H]-5-HT uptake was evaluated. The results are presented in the below Table 2.

10 **Table 2**

Uptake of [3H]-5-HT by synaptosomes from rat frontal cortex

| Compound | IC50 (μM) |
|------------|-----------|
| Compound A | 12 |
| Amperozide | 0.32 |
| Buspirone | 22 |
| FG5893 | 0.08 |

IC50 is the drug concentration which inhibit the uptake by 50 %.

15

Effects of drugs on alcohol intake.

To further illustrate the useful pharmacological properties of compounds of formula (I), the effect of Compound A administered systematically was determined in alcohol preferring (P) rats. Because of its pattern of drinking, the P animal seems to represent a valid genetically based model to approximate the human condition of alcoholism (McBride et al., Alcohol 7:199-205, 1990; Lankford et al., Pharmacol. Biochem. Behav. 8:293-299, 1991). After maximally preferred alcohol concentrations had stabilised for four days, Compound A in a dose of 2.5 and 10 mg/kg was administered twice a day over four consecutive days. Whereas control injections of saline

25

were without effect on alcohol consumption, during its administration both doses of Compound A significantly reduced the intake of alcohol in terms of both absolute g/kg and proportion of alcohol to total fluid intake. The highest dose of Compound A reduced intake of alcohol by >40 %. During the five days following administration of Compound A, the alcohol intakes of the rats rebounded, however, still being significantly lower than those of the pre-treatment level. Further, each dose increased the ingestion of food and water above pre-treatment levels during the period of injection. After Compound A injections, food and water returned to pre-drug levels.

The compounds of formula (I) and their acid addition salts are therefore indicated for use in amelioration of withdrawal symptoms and in modifying drug-seeking behaviour.

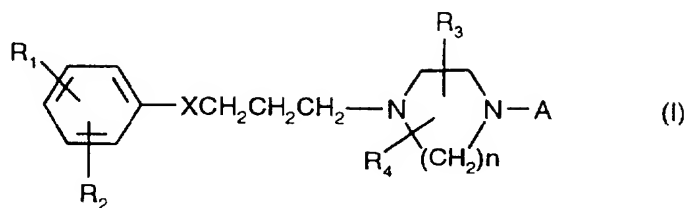
Effective quantities of the compounds of formula (I) and their acid addition salts are preferably administered to a patient in need of such treatment according to usual routes of administration and formulated in usual pharmaceutical compositions comprising an effective amount of the active ingredient and a suitable pharmaceutically acceptable carrier. Such compositions may take a variety of forms, e.g. solutions, suspensions, emulsions, tablets, capsules, and powders prepared for oral administration, patches for transdermal administration or sterile solutions for parental administration.

A suitable daily dose for use in the treatment of substance abuse disorders is contemplated to vary between 0.1 mg/kg to about 10 mg/kg body weight, in particular between 0.1 mg/kg to 2 mg/kg body weight, depending upon the specific condition to be treated, the age and weight of the specific patient, and the specific patient's response to the medication. The exact individual dosage, as well as the daily dosage, will be determined according to standard medical principles under the direction of a physician.

Various additives to enhance the stability or ease of administration of the drug are contemplated. The pharmaceutical composition may also contain additional therapeutically useful substances other than a compound of formula (I).

CLAIMS

1. Use of a compound of formula (I)



and the pharmaceutically acceptable acid addition salts thereof,

wherein

R1 is either halogen or hydrogen and R2 is halogen;

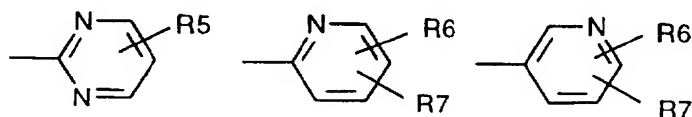
10 X is CH₂, O or S;

R3 and R4 are the same or different and selected from hydrogen or lower alkyl;

n is 2 or 3;

A is selected from the following pyrimidyl- or pyridyl-groups:

15



wherein

R5 is selected from hydrogen, lower alkyl or halogen;

20 R6 and R7 are the same or different and selected from hydrogen, lower alkyl,

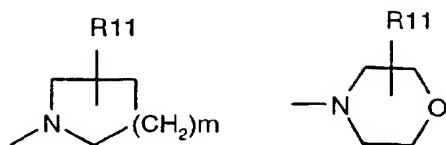
halogen, lower alkoxy, hydroxy, cyano, nitro, trifluoromethyl, COOR₈, CONR₉R₁₀ or COB;

wherein

25 R8 is hydrogen or lower alkyl;

R9 and R10 are the same or different and selected from hydrogen, lower alkyl and cycloalkyl;

B is selected from



5 wherein

m is 1, 2, 3, or 4;

R11 is selected from hydrogen or lower alkyl, and when used in the foregoing definitions the term lower alkyl is meant to include straight and branched hydrocarbon groups having from 1 to 5 carbon atoms;

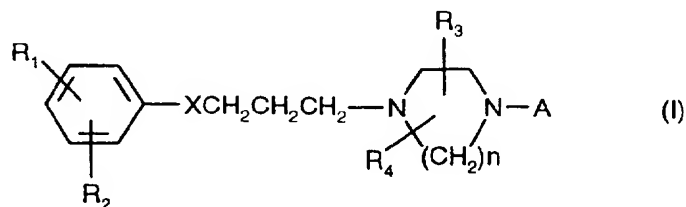
10 cycloalkyl is meant to include cyclohydrocarbon groups having from 3 to 8 carbon atoms;

lower alkoxy is meant to include straight and branched alkoxy groups having from 1 to 5 carbon atoms;

halogen is meant to include F, Cl and Br,

15 for the manufacture of a medicament for the relief or prevention of a withdrawal syndrome resulting from addiction to a drug or substance of abuse and/or for the suppression of dependence on drugs or substances of abuse.

20 2. A method for relief or prevention of a withdrawal syndrome resulting from addiction to a drug or substance of abuse and/or for the suppression of dependence on drugs or substances of abuse which comprises administering an effective amount of a compound of formula (I)



and the pharmaceutically acceptable acid addition salts thereof,
wherein

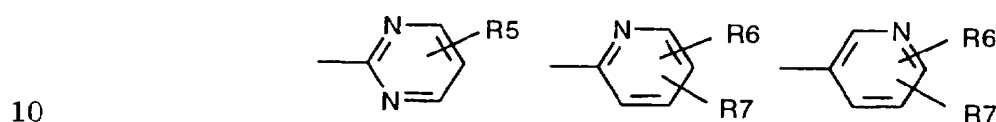
R1 is either halogen or hydrogen and R2 is halogen;

X is CH₂, O or S;

5 R3 and R4 are the same or different and selected from hydrogen or lower alkyl;

n is 2 or 3;

A is selected from the following pyrimidyl- or pyridyl-groups:



wherein

R5 is selected from hydrogen, lower alkyl or halogen;

15 R6 and R7 are the same or different and selected from hydrogen, lower alkyl,

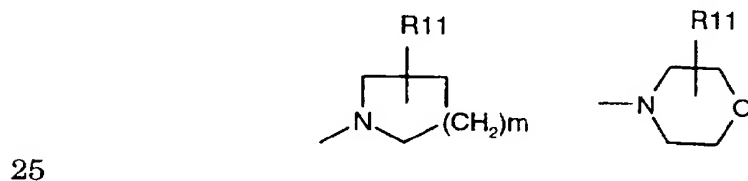
halogen, lower alkoxy, hydroxy, cyano, nitro, trifluoromethyl, COOR₈,
CONR₉R₁₀ or COB;

wherein

R₈ is hydrogen or lower alkyl;

20 R₉ and R₁₀ are the same or different and selected from hydrogen, lower alkyl and cycloalkyl;

B is selected from



wherein

m is 1, 2, 3, or 4;

R11 is selected from hydrogen or lower alkyl, and when used in the foregoing definitions the term lower alkyl is meant to include straight and branched hydrocarbon groups having from 1 to 5 carbon atoms;

5 cycloalkyl is meant to include cyclohydrocarbon groups having from 3 to 8 carbon atoms;

lower alkoxy is meant to include straight and branched alkoxy groups having from 1 to 5 carbon atoms;

halogen is meant to include F, Cl and Br.

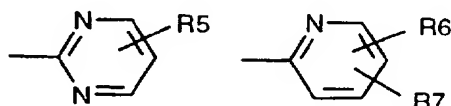
10 3. Use according to claim 1, wherein

R1 is hydrogen and R2 is halogen, especially F;

R3 and R4 are the same or different and selected from hydrogen or lower alkyl;

n is 2;

15 A is



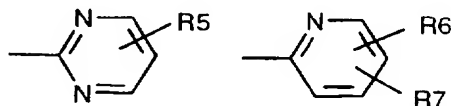
4. A method according to claim 2, wherein

20 R1 is hydrogen and R2 is halogen, especially F;

R3 and R4 are the same or different and selected from hydrogen or lower alkyl;

n is 2;

A is



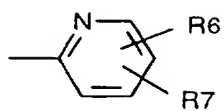
25

5. Use according to claim 1, wherein

R1 is hydrogen and R2 is F; X is CH₂;

R3 and R4 are hydrogen; n is 2;

A is

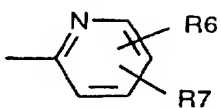


5 6. A method according to claim 2, wherein

R1 is hydrogen and R2 is F; X is CH₂;

R3 and R4 are hydrogen; n is 2;

A is



10

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 97/00673

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 31/495, A61K 31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| X | WO 9320821 A1 (KABI PHARMACIA AB), 28 October 1993 (28.10.93) -- | 1-6 |
| A | EP 0361271 A1 (PHARMACIA AB), 4 April 1990 (04.04.90) ----- | 1-6 |

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

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"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

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Date of the actual completion of the international search

20 August 1997

Date of mailing of the international search report

26 -08- 1997

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE97/00673

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 2, 4 and 6
because they relate to subject matter not required to be searched by this Authority, namely:
See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

06/08/97

International application No.
PCT/SE 97/00673

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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